REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-6, 8-11, 15-26, 28-43, 45-59 and 61-86, as well as newly introduced Claims 87-92, the only claims pending and under examination in this application.

Claims 1 and 9-11 have been amended to replace the phrase "the one or more intergenic regions are upstream of transcribed regions of the genomic DNA" with "is an intergenic fragment". Support for these amendments can be found in the specification, particularly in page 19, lines 22-25. Claims 1 and 9-11 have been amended to recite "wherein the sequences are across a portion of the genome of the cell". Claims 1, 9-11 and 71 have been amended to recite " the portion of the genome is examined to determine where the protein of interest binds". Support for these amendments can be found in the specification, particularly in page 11, lines 11-27. Claims 1, 8-11, 18, 21-23, 28, 32, 35-37, 49, 52-54, and 67-69 have been amended to make the language of these claims comport with the above amendments. Claim 71 has been amended to recite "wherein said sequences complementary to intergenic regions of genomic DNA of the cell are intergenic fragments and are across a portion of the genome of the cell". Support for this amendment can be found in the specification, particularly in page 11, lines 11-27 and page 19, lines 22-25. New Claims 87-89 have been added. Support for new Claims 87-89 can be found at page 12, lines 10-12 and page 32, lines 12-14. Support for new Claims 90-91 can be found at page 4, lines 3-4 and paragraph 15, lines 5 to 15. Support for new Claim 92 can be found at page 17, lines 9-11.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-6, 8, 10, 11, 17-22, 39-43, 45, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable

over Orlando et al. (Methods (1997) 11:205-214) in view of Schena et al. (Tibtech (1998) 16:301-306).

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The present invention as amended is directed to methods of identifying a region of a genome of a cell to which a protein of interest binds, whereby a portion of the genome is examined to determine where the protein of interest binds. Specifically, the methods of the invention involve amplifying a DNA fragment that binds to a DNA binding protein and combining the amplified DNA fragment with more than one sequences that are across a portion of the genome of the cell to identify the intergenic region of the genomic DNA of the cell where the protein of interest binds, whereby the portion of the genome is examined to determine where the protein of interest binds. An element of the claims is using "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**". The claim further specifies that intergenic fragments upstream of more than one transcribed region are employed.

Orlando et al. disclose crosslinking a multiprotein complex to *Drosophila* genomic DNA and selecting for certain chromatin-DNA complexes by immunoprecipitating with anti-Polycomb protein ("Pc protein") antibodies. Orlando et al. disclose that a stretch of genomic DNA covering all the exons and introns of the ultrabithorax and abdominal-A genes and the entire intergenic region between these two genes are protected (page 213, Figure 7). Orlando et al. do not teach that the Pc protein directly binds DNA and these results show neither any DNA binding sites nor any specific sites to which the Pc protein bind.

Besides the Pc protein data, Orlando et al. disclose the following: "We have adapted this method to the analysis of low-abundance DNA-binding transcription factors. . . . We were able to map their relative distribution over the genomic region of the *empty spiracles* gene and found a major binding site for all three proteins . . . ." (page 213, 2d col.; emphasis added.)

Orlando et al. do not teach or suggest using sequences that are across a portion of a genome, e.g., in the form of intergenic fragments from more than one transcribed region.

In contrast, the claimed methods use **sequences across a portion of the genome** to achieve a result where **a portion of the genome of the cell is examined to determine where the protein of interest binds**. Orlando et al. do not teach or suggest probing **sequences across a portion of the genome**; instead the disclosure is confined to the single *empty spiracles* gene. In fact Orlando et al. provide no teaching or suggestion as to how and with what nucleotide sequences they have used to identify the binding site of the transcription factors. Accordingly, Orlando et al. do not teach or suggest the claim element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**".

Schena et al. disclose a general review of microarray technology. Schena et al. also do not teach or suggest the claim element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**".

Accordingly, a *prima facie* case of obviousness has not been established because none of the cited references teach or suggest the element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**". For the reasons set forth herein and above, the Applicant respectfully requests the Examiner reconsider and withdraw this rejection over Orlando et al. in view of Schena et al.

Claims 1-6, 8-11, 15-22, 25, 26, 28-36, 39-53, 56-59, 61-68 and 71-84 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mercola et al. (USPN 6,410,233) in view of Schena et al.

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The present invention as amended is directed to methods of identifying a region of a genome of a cell to which a protein of interest binds. Specifically, the methods of the invention involve amplifying a DNA fragment that binds to a DNA binding protein and combining the amplified DNA fragment with a DNA microarray comprising more than one sequence complementary to more than one intergenic region of genomic DNA of the cell wherein each more than one sequence is an **intergenic fragment**. An element of the claims is the use of an intergenic fragment. The purpose of using the intergenic fragment is to identify the intergenic regions of the genomic DNA to which the DNA binding protein binds. An intergenic fragment is a fragment that covers sequences that are not in any open reading frames (ORF). The specification teaches that:

> "Array contains all non-overlapping open reading frames (ORF) . . . . When a sequence contains part or all of two potential reading frames, the larger sequence was chosen to represent the ORF. Any remaining sequence was included in intergenic fragments." (page 19, lines 22-25).

The Mercola '233 patent discloses probing cDNA arrays (Figure 1) or a cDNA library (col. 15, lines 1-5, 24-27, and 49-51). cDNA are DNA sequences constructed by the reverse transcription of RNA and necessarily include ORF sequences. Thus cDNA are not "intergenic fragments" which the specification defines as not including

any ORF sequences. Accordingly, the Mercola '233 patent does not teach or suggest the element of "**intergenic fragments**".

Schena et al. disclose a general review of microarray technology and do not teach or suggest the claim element of "**intergenic fragments**". Thus Schena et al. do not overcome the deficiency of the Mercola '233 patent.

Accordingly, a *prima facie* case of obviousness has not been established because none of the cited references teach or suggest the element of "**intergenic fragments**". For the reasons set forth herein and above, the Applicant respectfully requests the Examiner reconsider and withdraw this rejection over the Mercola '233 patent in view of Schena et al.

Claims 9, 15, 16, 25, 26, 28-36, 46, 47, 62, 63, 77 and 78 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Orlando et al. in view of Schena et al. and further in view of Hacia et al. (Nucleic Acids Research (1998) 26(16):3865-3866).

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

For the reasons set forth above, Orlando et al. and Schena et al. do not teach or suggest the element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**".

Hacia et al. disclose the use of a phycoerythrin•cy5 and phycoerythrin two color dye system in the mutational analysis of exon 11 of the *BRCA1* gene. Hacia et

al. do not teach or suggest the claim element "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**". Thus Hacia et al. do not overcome the deficiency of Orlando et al. and Schena et al.

Accordingly, a *prima facie* case of obviousness has not been established because none of the cited references teach or suggest the element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**". For the reasons set forth herein and above, the Applicant respectfully requests the Examiner reconsider and withdraw this rejection over Orlando et al. in view of Schena et al. and further in view of Hacia et al.

Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Orlando et al. in view of Schena et al. in view of Hacia et al. and further in view of Hallahan et al.

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

For the reasons set forth above, Orlando et al., Schena et al., and Hacia et al. do not teach or suggest the element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**".

Hallahan et al. disclose that human tumor cells transfected with dominant negative mutants of the c-*jun* and *Egr-1* transcription factors prevent the normal x-ray induction of gene constructs carrying binding sites of c-*jun* and *Egr-1*,

respectively. Hallahan et al. do not teach or suggest the claim element "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**".

Accordingly, a *prima facie* case of obviousness has not been established because Orlando et al., Schena et al. and Hacia et al. do not teach or suggest the element of "**sequences across a portion of the genome**" so that "**a portion of the genome of the cell is examined to determine where the protein of interest binds**", and there is no reasonable expectation of success in applying the mutant transcription factors of Hallahan et al. to the method of Orlando et al. For the reasons set forth herein and above, the Applicant respectfully requests the Examiner reconsider and withdraw this rejection over Orlando et al. in view of Schena et al. in view of Hacia et al. and further in view of Hallahan et al.

Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Mercola '233 patent in view of Schena et al. and further in view of Hallahan et al.

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

For the reasons set forth above, the Mercola '243 patent and Schena et al. do not teach or suggest the element of "**intergenic fragment**".

Hallahan et al. disclose that human tumor cells transfected with dominant negative mutants of the c-*jun* and *Egr-1* transcription factors prevent the normal x-ray induction of gene constructs carrying binding sites of c-*jun* and *Egr-1*,

respectively. Hallahan et al. do not teach or suggest the element of "**intergenic fragment**".

Accordingly, a *prima facie* case of obviousness has not been established because none of the cited references teach or suggest the element of "**intergenic fragments**". For the reasons set forth herein and above, the Applicant respectfully requests the Examiner reconsider and withdraw this rejection over the Mercola '233 patent in view of Schena et al. and in further view of Hallahan et al.

Double Patenting

Claims 1-6, 8-11, 15-26, 28-43, 45-59, and 61-86 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of Wyrick et al. (USPN 6,410,243) in view of Hacia et al. and further in view of Hallahan et al.

Accordingly, filed herewith is the requisite terminal disclaimer in view of which Applicants respectfully request these rejections be withdrawn.

Finally, new Claims 87-92 are patentable over the cited art for at least the reasons provided above.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10050560-1.

Respectfully submitted,
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Enclosure(s): Terminal Disclaimer over USPN 6,410,243

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